REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-11 and 15-19 are pending. Non-elected claims 15-17 were withdrawn from consideration by the Examiner. Applicants request rejoinder of withdrawn claims upon an indication that an elected claim is allowable.

The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. An informality is corrected in claim 4. Rewriting claim 16 does not change its scope, but merely clarifies the original intent of the Applicants to claim their invention. Neither amendment changes the scope of the claims. Support for new claims 18-19 is found at page 4, lines 29-34, of the specification.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1-11 were rejected under Section 102(b) as allegedly anticipated by Mitra et al. (U.S. Patent 5,955,105) as evidenced by HANDBOOK (*Handbook of Pharmaceutical Excipients, 5th Ed.*, pp. 134, 725 and 731) and MSDS (*Material Safety Data Sheet* for L-thyroxine, sodium salt). Applicants traverse because their claim 1 is directed to a pharmaceutical formulation comprising:

(a) an effective amount of levothyroxine sodium;

(b) microcrystalline cellulose having a mean particle size of less than 125 μm and present in an amount of 60 to 85% w/w, and

(c) pregelatinised starch present in an amount of 5 to 30% w/w.

It should be noted that pregelatinised starch is <u>not</u> water soluble. The *European Pharmacopoeia*, which is already of record, stated at page 1438 that pregelatinised starch swells in cold water. This clearly shows that it does not dissolve in water.

MITRA disclosed stabilised pharmaceutical preparations containing levothyroxine sodium. Stabilisation was achieved using a water-soluble glucose polymer (e.g., malto-dextrins at column 4, lines 15-16) and a partially soluble or insoluble cellulose polymer (see claim 1). Example 10 of MITRA used microcrystalline cellulose as the partially soluble or insoluble glucose polymer and starch as the water-soluble glucose polymer. Thus, the starch used by MITRA must be water-soluble starch.

The Examiner alleged at page 2 of the Office Action that the starch used in MITRA has a molecular weight of up to 160,000, and is therefore insoluble. Applicants respectfully refute this assertion because there was no such disclosure in MITRA. The only disclosure of starch with a molecular weight of up to 160,000 appears at column 4, lines 7-11, where it was disclosed that levothyroxine sodium is stable in connection with binders such as carbohydrates having a molecular weight of between 500 and 160,000. This statement, however, concerns what is known in the art: i.e., the previously known compositions of levothyroxine sodium. Then MITRA contrasted the previously known compositions with the invention that was being claimed, saying, in lines 14-21, that "it is surprising that soluble glucose polymers . . . when used in combination with the insoluble or partially soluble cellulose polymers, result in a dosage composition that has improved and superior stability, content uniformity, good tableting and dissolution properties" (emphasis added). This summary of MITRA's invention clearly showed that the glucose polymer used in Example 10 was soluble. In addition, all of the independent claims of MITRA, which define the scope of MITRA's claimed invention, require that the glucose polymer or polysaccharide is water soluble. The latter is an essential feature of MITRA's invention. Thus it is clear that the starch used in Example 10 of MITRA must be water soluble to fall within the scope of the invention claimed therein.

The Examiner also asserted that the starch used in Example 10 is synonymous with pregelatinised starch. In particular, he argued that pregelatinised starch and starch are synonymous with each other because they have the same CAS registry number, empirical formula, and structural formula. While the CAS registry number, and empirical and structural formulae, are the same for starch and pregelatinised starch, they have a number of different chemical and physical properties. Pregelatinised starch contains 5%

of free amylose and 15% of free amylopectin. In addition to unmodified starch, pregelatinised starch has enhanced flow and compression properties as compared to MITRA's starch. Pregelatinised starch granules occur as either irregular chunks or thin flakes, whereas MITRA's starch occurs as a powder comprising very small spherical or ovoid granules. In any case, MITRA's starch is a water-soluble starch, and individual water-soluble starches such as maltodextrin, β-cyclodextrin, and hydroxypropyl-β-cyclodextrin have unique CAS registry numbers (9050-36-6, 7585-39-9, and 128446-35-5, respectively), and different empirical and structural formulae as compared to the pregelatinised starch required by Applicants' claims.

Accordingly, since the pharmaceutical formulations of Applicants' claims include pregelatinised starch, which is not water soluble, whereas MITRA disclosed pharmaceutical formulations including a water-soluble glucose polymer, novelty is established. Specifically, the formulation of Example 10 includes water-soluble starch. Therefore, the claims of the present application are not anticipated by MITRA. Applicants submit that this feature of their claimed invention (i.e., pregelatinised starch is not water soluble) is sufficient to distinguish over the cited document so any other incorrect allegations about its disclosure are not disputed here, but the opportunity to dispute them in the future is reserved.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge

possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. A claim directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-11 were rejected under Section 103(a) as allegedly unpatentable over MITRA as evidenced by HANDBOOK and MSDS in view of EDQM (*European Pharmacopoeia*, pg. 1438) Franz et al. (U.S. Patent Publ. 2003/0032675). Applicants traverse.

The failure of MITRA to disclose the claimed invention as discussed above is not remedied by the attempt to combine that disclosure with EDQM and FRANZ. MITRA disclosed stabilised pharmaceutical preparations containing levothyroxine sodium (column 1, lines 12-14), a water-soluble glucose polymer (e.g., maltodextrin at column 4, lines 15-16), and a partially soluble or insoluble cellulose polymer (see claim 1). In Example 10 of MITRA, the partially soluble or insoluble cellulose polymer is microcrystalline cellulose and the water-soluble glucose polymer is starch: i.e., water-soluble starch.

In contrast, Applicants' claims differ from what is disclosed in MITRA (particularly Example 10 therein) in that the present invention employs pregelatinised starch instead of water-soluble starch. As noted above, pregelatinised starch is <u>not</u> water soluble.

FRANZ disclosed an apparatus and a method for manufacturing thyroid hormone preparations, such as levothyroxine sodium, in tablet form. It did not discuss the nature of the excipients used in the levothyroxine sodium tablets, nor the amounts of excipients, nor how such excipients can affect the stability and disintegration characteristics of the tablets. It merely disclosed a number of commercially available formulations of levo-

thyroxine sodium identified by their tradenames: i.e., Levoxyl, Synthroid, Unithroid, and Soloxine (see page 1, left column, fourth paragraph). Claim 6 of FRANZ recites a formulation of levothyroxine sodium, lactose, microcrystalline cellulose, pregelatinised starch, and magnesium stearate. But no quantities of the various excipients were provided, and there was no suggestion that this combination has any particular advantage over other commercially available formulations of levothyroxine sodium. Moreover, no evidence was presented that it would have been obvious to modify the formulation in Example 10 of MITRA by using the specific excipients of FRANZ's specific formulation in claim 6 with a reasonable expectation of success. Further, since MITRA makes it essential to use a water-soluble glucose polymer, one of ordinary skill in the art would not have had a reason to consider obvious its replacement by pregelatinised starch (i.e., a water-insoluble glucose polymer). Finally, Applicants note out that Example 10 of MITRA is not disclosed as a preferred embodiment – the preferred embodiments contain β-cyclodextrin, hydroxypropyl-β-cyclodextrin, or especially maltodextrin (see column 3, lines 52-57) – and one of ordinary skill in the art would have had no reason to single out Example 10 for use as the starting point for modifying the formulation. In fact, MITRA teaches away from Applicants' claimed invention because the cited document requires use of a water-soluble glucose polymer instead of pregelatinised starch, which is not soluble in water.

Even if one of ordinary skill in the art were to combine what is disclosed by claim 6 of FRANZ and Example 10 of MITRA, there is no suggestion in either document that such a combination would lead to a formulation having the particularly advantageous stability and disintegration characteristics as disclosed in the present application (see data and discussion on pages 7-11 of the specification under "Conclusions"). Thus it is submitted that Applicants' claims are not obvious over the cited documents. Applicants submit that these features of their claimed invention are sufficient to distinguish over the cited documents so any other incorrect allegations about their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved.

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinarily skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /Gary R. Tanigawa/
Gary R. Tanigawa
Reg. No. 43,180

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100